Ageing in reverse: Twin cycle hypothesis and 3Rs as catalysts for transformative longevity

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ABSTRACT

Introduction: Malaysia's shift toward an ageing nation status, expected to exceed 15% of the population aged 60 and above by 2030, demands a strategic shift from reactive healthcare to anticipatory, person-centred models. Healthy ageing requires a multidisciplinary involvement of biomedical innovation, digital solutions, and culturally grounded wellness practices to combat the rising burden of metabolic syndromes. Research indicates that visceral fat contributes to systemic inflammation, insulin resistance, and dyslipidaemia, which can lead to hypertension and diabetes. At the core of this review lies the Twin Cycle Hypothesis, which highlights the central role of hepatic and pancreatic fat in the potentially reversible pathogenesis of Type 2 Diabetes. When reinterpreted through the lens of the 3Rs - Rehabilitation, Reversal, and pRolonging age (health span extension), this biological model evolves into a conceptual framework for advancing metabolic resilience in older people. While such integrative approaches have been implemented in Newcastle University and the National Health Service (United Kingdom), they are yet to be established in Malaysia. We propose reviewing and adapting this model to local ageing frameworks to target visceral fat reduction and metabolic recovery. **Materials and Methods:** This review employed a narrative synthesis of peer-reviewed articles, policy documents, and international reports published from inception till 2025. The literature search was conducted using PubMed with the following keywords: ("twin-cycle" OR "twin cycle") AND ("Diabetes Mellitus"[MeSH] OR "type 2 diabetes" OR "non-insulin dependent diabetes" OR "diabetes" OR "prediabetes" OR "T2DM" OR "DMT2"). All relevant papers were pooled accordingly for data extraction. **Results:** A total of 13 articles were pooled, predominantly originating from the United Kingdom (UK), with Professor Roy Taylor emerging as the most prominent contributor. The Twin Cycle Hypothesis, first introduced in 2008, posits that excessive caloric intake leads to triacylglycerol accumulation in the liver and pancreas, triggering insulin resistance and β-cell dysfunction. This hypothesis was also confirmed via magnetic resonance spectroscopy. In healthy individuals, triglycerides are safely stored in subcutaneous tissue; however, in disease states, ectopic fat and lipid intermediates accumulate in visceral organs, disrupting metabolic regulation. Rehabilitation and reversal typically involve a structured low-calorie diet (~800 kcal/day), sustained weight loss of 10–15 kg, and behavioural reprogramming to restore hepatic insulin sensitivity and reduce pancreatic fat. Clinical trials in the UK have also affirm the plausibility of diabetes remission via intensive weight loss and low-calorie diet. These interventions have been shown to prolong health span by restoring metabolic function, reducing medication burden, and improving quality-adjusted life years. While Malaysia lacks an official remission pathway, we propose adapting the UK's Newcastle–NHS model by embedding motivational interviewing, culturally adapted dietary guidance, alongside digital health integration. **Conclusion:** Reframing and integrating the Twin Cycle Hypothesis with the 3Rs promotes well-being among the ageing population in Malaysia. Rather than solely controlling glycaemic levels, lifestyle interventions such as weight loss and a low calorie-diet should be prioritised and personalised for patient-centred care into primary and secondary care.

Keywords: Twin Cycle Hypothesis, fatty liver, fatty pancreas, diabetes reversal, longevity